THE REMARKS

Claim Amendment

The specification is amended to capitalize all trademarks with the generic description followed.

The sequence ID numbers of gamma-Catenin, Ep-Cam, E-Cadherin, alpha-Catenin 1, alpha-Catenin 2, beta-Catenin, Involucrin, CK8, CK18, CK10, CK13, p120, $p16^{INK4a}$, and p14ARF are inserted in the specification. The paper sequence listing is inserted at the end of the specification. Support for the amendments is found in the attached printout from NCBI website, which lists each protein name as identified in the application, its accession number, and its sequence.

The amendment at page 41, line 5, which inserts 2μg/ml, is supported by the parent application EP 02017313.4.

Claim 33 is amended to recite preparing a sample solution by solubilizing a human cervical sample in a lysis buffer. Support for the amendment can be found at page 11, line 27. Claim 33 is also amended to recite determining the adequacy of the sample by comparing the levels of the normalization markers detected within the sample solution with threshold levels of the normalization markers. Support for the amendment can be found at page 20, lines 15-27. Claim 33 is further amended to recite whereby when the sample is adequate, the positive level of the relevant marker is indicative of cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia. Support for the amendment can be found at page 41, line 29 through page 42, line 10 and page 45, line 17 through page 46, line 20.

Claims 34, 35, 39 and 40 are amended to recite sequence ID numbers.

New Claim 52 is supported by page 40, line 5.

No new matter is introduced in any of the above amendments.

Objection to the Specification

Applicants have amended the specification to capitalize the trademark names with the generic description followed.

35 USC § 112, second paragraph rejections

Claims 33-37 , 39, and 40 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for allegedly failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention.

(a) (1) Claims 33-37, 39, and 40 were directed to a process for diagnosing cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia.

Applicants have amended the claims to recite a process for diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia.

(a) (2) The Examiner states that it cannot be determined how the determination of adequacy of the sample and the diagnosis of disease are necessarily "based" on the level of the normalization marker and/or $p16^{INK4a}$.

Applicants have amended Claim 33 to recite determining the adequacy of the sample by comparing the levels of the normalization markers detected within the sample solution with threshold levels of the normalization markers; and to recite whereby when the sample is adequate, the positive level of the relevant marker is indicative of cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia.

(b) Claims 34, 35, 39, and 40 are allegedly indefinite because the claims use "$p16^{INK4a}$", "p14ARF", "gamma-catenin", "Ep-Cam", "E-cadherin", "alpha-catenin", "beta-catenin", "Involucrin", "CK8", "CK18", "CK10", "CK13", and "p120" as the sole means of identifying the polypeptides to which the claims refer.

Applicants have amended the specification to include the sequences of each protein, and amended the claims to identify the proteins by the sequence ID numbers.

35 USC § 112, First Paragraph Rejection – Written Description

Claims 34, 35, 39, and 40 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner states that the claims are directed to one or more polypeptides (i.e., *markers*) identified by the designations "$p16^{INK4a}$ ", "p14ARF", "gamma-catenin", "Ep-Cam", "E-cadherin", "alpha-catenin", "beta-catenin", "Involucrin", "CK8", "CK18", "CK10", "CK13", and "p120". However, because of the use of such nomenclature alone, it cannot be determined to which particular polypeptide(s) the claims are directed.

Applicants have amended the specification to include the sequences of each protein, and amended the claims to identify the proteins by the sequence ID numbers.

35 USC § 112, First Paragraph Rejection – Enabling

Claims 34-37, 39, and 40 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for using a process for diagnosing cervical dysplasia or cervical cancer, said process comprising detecting the level of expression $p16^{INK4a}$, does not allegedly provide enablement for using a process for diagnosing any type of cervical intraepithelial neoplasia.

The Examiner cites Klaes and states that no detectable expression was observed in low-grade cervical lisions (CIN I) associated with low-risk HPV types. This is incorrect. In Kaes (copy attached), Table 1 (page 279) shows there were 15 cases of low-risk HPV type tested. Among them, 7 (47%) were negative, 2 (13%) had sporadic p16 stains, and 6 (40%) had focal p16 stains. Therefore, 53% of the low-risk HPV cases tested were p16 positive.

Among the 47 cases of CIN I tested, 40 samples (85%) had sporadic, focal, or diffuse p16 stains; only 7 samples (14%) were negative. Therefore, Applicants have enabled a method for detecting cervical intraepithelial neoplasia, including CIN I.

35 USC § 103 (a) Rejection

Claims 33, 34, 36, and 37 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Bibbo et al. (*Acta Cytologica*. 2002 Jan-Feb; **46** (1): 25-29) and Grundhoefer et al. (*Bytometry*. 2001 Dec 15; **46** (6): 340-344).

Bibbo et al. disclose procedures for immunocytochemical detection of p16 antigen in thin-layer, liqiuid-based cytology specimens. The specimens contained whole cells, and were not

solubilized by a lysis buffer. (see Materials and Methods at page 26). A lysed cell solution would not work for immunocytochemical detection, and it would render the cited reference unsatisfactory for its intended purpose.

Although Bibbo et al. in a single sentence described that a sampling error might be responsible for the negative staining result, Bibbo et al. did NOT suggest how to avoid the sampling error. Bibbo et al. did not mentioned determining adequacy of the sample, let alone how to determine the adequacy of the sample.

Grundhoefer et al. disclose determining cervical cytology specimen adequacy using cellular light scatter and flow cytometry. The method used cell suspensions containing whole cells, not lysed cells solution. A lysed cell solution would not work by the method of light scattering, and it would render the cited reference unsatisfactory for its intended purpose.

In the present method, a cervical sample is first solubilized in a lysis buffer and thus all the morphology data of the sample are lost by lysis. However, Applicants have discovered that data, which are lost through lysis of the material, are contained within the sample solution encoded by the levels of molecule markers and can be reconstructed using molecular data for normalization to the respective morphologic characteristics. By determining the levels of relevant markers and normalization markers in the lysed, solubilized sample, the disadvantage of loss of information through lysis of the sample is overcome. (See Application at page 6, line 22, through page 7, line 8).

Therefore, the present method is totally different from Bibbo et al. and Grundhoefer et al., and the 35 USC § 103(a) rejection of Claims 33, 34, 36, and 37 should be withdrawn.

Claims 35, 39, and 40 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bibbo et al. (*Acta Cytologica*. 2002 Jan-Feb; **46** (1): 25-29) and Grundhoefer et al. (*Bytometry*. 2001 Dec 15; **46** (6): 340-344), as applied to claims 33, 34, 36, and 37 above, and further in view of Levy et al. (differentiation. 1988 Dec; 39 (3): 185-196).

Levy et al. disclose subtyping of epithelial cells of human uterine cervix using cytokeratine antibodies. Levy et al. do not cure the deficiency of Bibbo et al. and Grundhoefer et al.

Therefore, the 35 USC § 103(a) rejection of Claims 35, 39, and 40 should be withdrawn.

Request for Telephone Interview

Applicants believe that the application is now in good and proper condition for allowance. In the event that the Examiner does not find Applicants' argument persuasive, Applicants request that the Examiner telephones the undersigned attorney to discuss the issues to further the allowance of the application.

Respectfully submitted,

Date: July 18, 2007

Viola T. Kung, Ph.D.
Reg. No. 41,131

HOWREY LLP
2941 Fairview Park Drive
Box 7
Falls Church, VA 22042
Ph. (650) 798-3570
Fax (650) 798-3600

Enclosures: Klaes, et al. *Int. J. Cancer*, 92: 276-284 (2001)
NCBI Sequences of gamma-Catenin, Ep-Cam, E-Cadherin, alpha-Catenin 1, alpha-Catenin 2, beta-Catenin, Involucrin, CK8, CK18, CK10, CK13, p120, $p16^{INK4a}$, and p14ARF.